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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/884,873	06/30/1997	PHILLIP DAN COOK	ISIS-2202	6678

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EXAMINER

BAKER, MAURIE GARCIA

ART UNIT PAPER NUMBER

1639

DATE MAILED: 11/21/2003

39

Please find below and/or attached an Office communication concerning this application or proceeding.

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# Office Action Summary

Application No.  
**08/884,873**

Applicant(s)

Cook

Examiner  
**Maurie G. Baker, Ph.D.**

Art Unit  
**1639**

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on Sep 26, 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 2-5, 7, and 33 is/are pending in the application.
- 4a) Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2-5, 7, and 33 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some\* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\*See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_ 6) ☐ Other:

### **DETAILED ACTION**

1. The Response filed September 26, 2003 (Paper No. 38) is acknowledged. Claim 5 was amended, claims 8-12 were cancelled and no claims were added. Thus, currently, claims 2-5, 7 and 33 are pending and under examination.

#### ***Status of Rejections***

2. The previous rejections under 35 U.S.C. 112, second paragraph are withdrawn in view of applicant's amendments, cancellation of claims and arguments. The rejection under 35 U.S.C. 103(a) is maintained and applicant's arguments are addressed following the rejection.

#### ***Maintained Rejections*** ***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 2-5, 7 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Usbeck et al (JACS, 1961, Vol. 83, pp. 1113-1117) in view of Gordeev et al (WO 96/33972; of record) and Gordon et al (J. Med. Chem. 1994; of record).

Usbeck et al teach 8-triazenopurine nitrogen mustards that read on the claimed compounds having structure II (see page 1114, for example). These compounds are labeled “potential purine antagonists” and their biological activity is discussed (page 1113 and page 1115, 1<sup>st</sup> column, last paragraph). The triazenopurine compounds have least three functionalizable atoms on the purine scaffold (reading on instant claims 5 and 7). The compounds of the reference have groups that read on the claimed tethers, T where the tethers have least one functionalizable atom which is nitrogen, oxygen and/or sulfur and also on the claimed chemical substituents, L. Specifically considering the compounds of the reference in Tables I – III and page 1114, 2<sup>nd</sup> column of the reference, at least 10 compounds that read on the claimed structure II are shown. The compounds read on those claimed when  $j=1$ ,  $e=0$ , T is O or NH and L is H for two of the T-L combinations and for the other T-L combination, T is -N=N- and L is N-dialkyl, aryl or thioalkyl.

Usbeck et al lacks the teaching of specifically creating a *mixture* of at least 6 compounds.

However, Gordeev et al teach libraries of heterocyclic (pyrimidine) compounds, see Abstract. The library compounds of Gordeev et al have a heterocyclic scaffold (see page 34-35 and more specifically page 81) and are substantially homogeneous (page 35, bottom). The library compounds are made in a pooled format (see page 84, lines 18-28), for example, a pool of 21 pyrimidines is made and tested. This reads on the limitation of a mixture of at

least 6 compounds and the further limitations of claims 2 and 3. All compounds are present in at least some of the pools and the compounds are synthesized at a purity (see page 81) where the mixture would be close to equimolarity, reading on the limitations of claim 4.

Also, Gordon et al teaches that “[w]hen small molecule leads for a target have been previously defined...the notion of searching for more potent derivatives among libraries combinatorially enriched in specific pharmacophore analogs is an obvious tactic to pursue” (page 1386 1<sup>st</sup> column, 1<sup>st</sup> full paragraph). Gordon et al additionally teaches the general principles of combinatorial chemistry and the rationale for creating libraries, see page 1385 and 1397-1401 generally. Specifically, the notion of intentional biasing as a form of drug design is taught (see page 1401, 1<sup>st</sup> column). Gordon et al teaches a “spectrum of molecular diversity” (see page 1397, Figure 19) that describes why a library of a certain size would be useful for a variety of different applications.

Therefore, it would have been *prima facie* obvious to one of ordinary skill to create a mixture (i.e. library) of six or more compounds of the claimed type based on the teachings Usbeck et al as to the synthesis and uses of such compounds and the teachings of Gordeev et al and Gordon et al regarding libraries. A person of ordinary skill in the art would have been motivated to create libraries to have large numbers of molecules available for testing for improved properties (see Gordon, page 1398, 1<sup>st</sup> paragraph). A person of ordinary skill in the art would have been motivated to specifically create a

mixture (i.e. pooled format) as Gordeev et al teaches the creation of libraries of heterocyclic compounds using this format.

### *Response to Arguments*

5. Applicant's arguments filed September 26, 2003 have been fully considered but are not found persuasive. The examiner's rationale is set forth below.

6. Applicants main argument is that there is "no substituent of formula L that is found or suggested by the Usbeck reference" (Response, page 6). The examiner respectfully disagrees. As stated in the rejection, the reference clearly teaches compounds that are within the scope of the instant structure II. See the following, reiterated from the rejection:

Specifically considering the compounds of the reference in Tables I – III and page 1114, 2<sup>nd</sup> column of the reference, at least 10 compounds that read on the claimed structure II are shown. The compounds read on those claimed when j=1, e=0, T is O or NH and L is H for two of the T-L combinations and for the other T-L combination, T is -N=N- and L is N-dialkyl, aryl or thioalkyl.

It is noted for the record that it is clear in the Usbeck reference that the notation -C-C-X denotes an ethyl (alkyl) chain attached to X. To explain further, taking, for example, the fifth compound in Table I of the reference, this compound clearly reads on the instant structure II when T is O and L is H for two of the T-L combinations and for the other T-L combination, T is -N=N- and L is N-dialkyl (N-dialkyl is clearly a member of the Markush group for L). The N-dialkyl group of Usbeck consists of the N attached to the -N=N-, R<sub>3</sub> (one alkyl group, in this instance CH<sub>3</sub>) and -C-C-X (the other alkyl group, in this instance CH<sub>2</sub>CH<sub>2</sub>Cl). It is clear from the instant specification that substituted alkyl

groups are encompassed by the term “alkyl” (see, e.g. instant specification page 15, line 32 – page 16, line 16).

7. In response to applicant’s argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

8. In this case, the examiner maintains that the *combined* teachings of the cited references render the claimed invention obvious. The teachings referred to in the rejection are strong motivation. Also, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). In the instant case, the beneficial result of the combination of references the creation of libraries to have large numbers of molecules available for testing for improved properties.

9. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The examiner maintains that the combined teachings of the cited references indicate information that was within the level of ordinary skill and render the claimed invention *prima facie* obvious.

10. For these reasons and the reasons of record, the above rejection under 35 U.S.C. 103(a) is maintained.

***Status of Claims/Conclusion***

11. No claims are allowed.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the



advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maurie Garcia Baker, Ph.D. whose telephone number is (703) 308-0065. The examiner is on an increased flextime schedule but can normally be reached on Monday-Thursday and alternate Fridays from 9:30 to 7:00.

14. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew J. Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maurie Garcia Baker, Ph.D.  
November 19, 2003



**MAURIE GARCIA BAKER PH.D.**  
**PRIMARY EXAMINER**